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Datasheet for the decision of 11 April 2017

Case Number: T 0858/13 - 3.3.04

Application Number: 05777592.6

Publication Number: 1732949

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Language of the proceedings: EN

Title of invention:
Methods for treating bone cancer pain by administering a nerve growth factor antagonist

Patent Proprietors:
Rinat Neuroscience Corp.
Regents of the University of Minnesota

Opponents:
Regeneron Pharmaceuticals, Inc.
Adams, Harvey Vaughan John
Sanofi-Aventis U.S. Inc.

Headword:
Antagonistic anti-NGF antibodies for use in bone cancer pain treatment/RINAT NEUROSCIENCE, REGENTS OF THE UNIVERSITY OF MINNESOTA

Relevant legal provisions:
EPC Art. 56
RPBA Art. 13(1)

Keyword:
Main request: Inventive step (no)
Admission of auxiliary requests filed during oral proceedings (no)

Decisions cited:

Catchword:

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Case Number: T 0858/13 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 11 April 2017

Appellants I: (Joint Patent Proprietors)	Rinat Neuroscience Corp. 230 East Grand Avenue South San Francisco, CA 94080 (US)
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Decision under appeal:

Interlocutory decision of the Opposition Division of the European Patent Office posted on 14 January 2013 concerning maintenance of the European Patent No. 1732949 in amended form.

Composition of the Board:

Chairwoman G. Alt
Members: M. Montrone
M. Blasi

Summary of Facts and Submissions

I. Appeals were lodged by the patent proprietors, opponent 01 and opponent 02 (hereinafter "appellants I", "appellant II" and "appellant III", respectively) against the interlocutory decision of the opposition division that European patent No. 1 732 949, having the title "*Methods for treating bone cancer pain by administering a nerve growth factor antagonist*", could be maintained in amended form.

II. In the impugned decision, the opposition division held that opponent 03's opposition was inadmissible and that the subject-matter of claims 1 of the main request and auxiliary requests 1 to 7 lacked novelty, while auxiliary request 8 submitted during the oral proceedings met the requirements of the EPC.

III. Appellants I submitted a main request (patent as granted) and six auxiliary requests with their statement of grounds of appeal, and auxiliary requests 7 and 8 with their reply to appellants II and III's statements of grounds of appeal. The main request was identical to the main request underlying the impugned decision.

Claim 1 of the main request reads:

"1. Use of a nerve growth factor (NGF) antagonist in the manufacture of a medicament for treating bone cancer pain in an individual, wherein the NGF antagonist is an anti-NGF antagonist antibody."

IV. Appellants II and III with their reply to appellants I's statement of grounds of appeal submitted *inter alia* arguments why the subject-matter of claim 1 of the main request lacked an inventive step.

V. The parties were summoned to oral proceedings. Appellant III in reply informed the board in a letter that it would not be attending the oral proceedings.

VI. In the course of the oral proceedings before the board, held on 11 April 2017 in the absence of duly summoned appellant III, appellants I withdrew auxiliary requests 1 to 8 and submitted new auxiliary requests 1 and 2. At the end of the oral proceedings the chairwoman announced the board's decision.

VII. The following documents are cited in this decision:

A9: US 5,147,294

A6: WO 02/096458

A7: Ro *et al.*, Pain, 79: 265-274, 1999

A10: Zhu *et al.*, J. Clin. Oncol., 17(8): 2419-2428, 1999

A11: Schwei *et al.*, J. Neuroscience, 19: 10866-10897, 1999

A12: Cain *et al.*, J. Neurophysiol., 85: 1561-1574, 2001

A13: Mantyh *et al.*, Nature Reviews, Cancer, 2: 201-209, 2002

A14: Jongen *et al.*, Neuroscience, Abstract, Presentation Number 52.20, November 3, 2002

A25: Honore *et al.*, Neuroscience, 98, 585-598, 2000

A27: Clohesy *et al.*, Cancer Suppl., 97: 866-873, 2003

A28: Gwak *et al.*, Neuroscience Letters, 336: 117-120, 2003

A32: Van Rossum *et al.*, Neuroscience and Behavioural Rev., 21, 649-678, 1997

A34: Declaration of Prof. Mantyh, dated 23 January 2012

A36: Mach *et al.*, Soc. Neuroscience, 26, Abstract 734.1, 2000

A37: Averill *et al.*, Europ. J. of Neuroscience, 7, 1484-1494, 1995

A48: Goodman and Gilman, The Pharmacological Basis of Therapeutics, 10th ed., 1417-1419, 2001

VIII. Appellants I's arguments, as far as they are relevant to the present decision, may be summarised as follows:

Main request

Inventive step (Articles 100(a) and 56 EPC)

Document A9 represented the closest prior art. It disclosed the administration of sympathetic nerve blockers in a first step followed by the administration of the chemotherapeutic agent vincristine in the treatment of two human patients suffering from bone

cancer pain (see "*Case History 1*" and "*Case History 2*"). The subject-matter of claim 1 differed therefrom in that instead of vincristine an antagonistic anti-nerve growth factor (NGF) antibody was administered. This antibody acted specifically on NGF, thus causing fewer adverse side-effects compared to vincristine. Moreover, it provided a more effective attenuation of chronic and movement-evoked bone cancer pain compared to morphine (see patent, Examples 2 and 3). In view of these benefits, the objective technical problem was the provision of an improved therapy for bone cancer pain.

The skilled person seeking such an improved therapy and starting from the treatment scheme disclosed in Case History 1 and 2 of document A9, would not have contemplated the use of an antagonistic anti-NGF antibody in the claimed therapeutic application, since he would not have considered that vincristine's demonstrated efficacy was caused by an NGF antagonism.

The skilled person would arrive at this view because vincristine was only administered for "*approximately four calender days*" (see Case History 1, column 28, lines 2 to 5), which, in view of its known short biological half-life of about 20 hours (see document A48, page 1418, column 1, last paragraph), taught the skilled person that - if vincristine were to act on NGF - a few days after concluding the treatment its serum concentration was already too low to significantly inhibit NGF's stimulatory effect on neurons. Thus, the skilled person would have derived from the treatment scheme disclosed in Case History 1 of document A9 that vincristine's potential antagonising effect on NGF was relatively short-lasting, which was however inconsistent with the reported nine-month pain-free

state of the patient after concluding the treatment (see column 28, lines 14 and 15).

In view of this discrepancy, the skilled person would have looked for other mechanisms of action that could possibly underlie vincristine's reported efficacy in reducing bone cancer pain. Thus, he would have considered that vincristine's cytotoxic activity on tumours (see document A9, column 24, line 67, to column 25, line 8) and neurons (see document A48, page 1419, column 1, third full paragraph), causing a tumour size reduction and damages of the nerves, were responsible for the observed pain reduction since both effects were rather long-lasting and thus better matched with the patient's reported long pain-free state.

In view of these considerations, the skilled person would not have considered NGF to be a target in the treatment of bone cancer pain, and consequently would not have derived pointers from the teaching of document A9 that antagonistic anti-NGF antibodies could be potentially beneficial in treating bone cancer pain.

Pointers to NGF being a target in the claimed therapeutic application were also not derivable from other relevant prior art documents cited.

Firstly, these documents suggested many different potential therapeutic targets (see e.g. document A13, Table 2), without disclosing NGF (see e.g. documents A27, page 869, column 1, second paragraph, to page 870, column 2, first paragraph, and A34, point 4).

Secondly, at the relevant date of the patent, the skilled person knew that bone cancer pain was unique compared to other states of pain, because

(i) analgesics that were efficacious in the relief of inflammatory or neuropathic pains were mostly ineffective (see documents A11, page 10895, column 1, third paragraph, and A27, page 867, column 1, first paragraph) and (ii) the spinal cord and sensory neurons in an animal model of bone cancer pain exhibited a protein signature not seen in other pain states (see e.g. document A25, abstract). This demonstrated clinical and biochemical uniqueness of bone cancer pain would have significantly reduced the skilled person's expectation of success for anti-NGF antibodies as agents in the claimed therapeutic application, irrespective of their proven efficacy in alleviating inflammatory or neuropathic pain states.

Thirdly, the biochemical mechanism underlying bone cancer pain including its neural transmission was unknown at the relevant date of the patent. Thus, document A14 provided no pointers that NGF was involved in this unique pain state, although it reported that NGF was expressed *in vitro* and *in vivo* in a particular bone cancer cell line and that calcitonin gene-related peptide (CGRP)-immunoreactive nerve fibres were surrounded by tumour cells. An involvement of CGRP-immunoreactive nerve fibres in the transmission of bone cancer pain was also not derivable from the disclosure in documents A25 (see page 595, column 1, second paragraph, to column 2, first paragraph), A32 (see abstract), A34 (see point 5), A36 (see abstract) and A37 (see Figure 8).

Admission of auxiliary requests 1 and 2 into the appeal proceedings

The filing of auxiliary requests 1 and 2 was a direct response to the board's finding that the objective technical problem in view of the closest prior art underlying the subject-matter of claim 1 of the main request was the provision of an alternative and not an improved treatment for bone cancer pain. This outcome could not have been foreseen. The issue was specifically addressed by the introduction of new features taken from the description into claims 1 of both requests.

IX. The arguments of appellants II and III, as far as they are relevant to the present decision, may be summarised as follows:

Main request

Inventive step (Articles 100(a) and 56 EPC)

Document A9 or A14 represented the closest prior art.

Document A9 disclosed a central role of NGF in the initiation and maintenance of chronic pain states, which was mediated by the persistent stimulation of neurons into a hyperactive state (see columns 10 to 12). Thus, the treatment of chronic pain disclosed in this document relied on the administration of at least one antagonist of NGF in combination with a local sympathetic analgesic. The document disclosed various equally preferred NGF antagonists for this purpose, including the vinca alkaloid vincristine and neutralising anti-NGF antibodies (see columns 22 and 23). Furthermore, the document disclosed two clinical

studies with human patients (see Case Histories 1 and 2) that demonstrated the efficacy of vincristine in combination with a local anaesthetic in alleviating bone cancer pain.

Document A14 suggested the involvement of NGF in the transmission of bone cancer pain, based on the finding that NGF was released *in vitro* and *in vivo* from a bone cancer cell and the observation that primary afferent CGRP-immunoreactive nerve fibres - that were frequently sensitised by NGF - were surrounded by tumour cells in tumour-bearing femora.

The subject-matter of claim 1 differed from the treatment disclosed in Case Histories 1 and 2 in document A9 in that a neutralising anti-NGF antibody was used as an antagonist of NGF instead of vincristine. The results obtained with the mouse model in the patent could not be directly compared with those obtained in human patients disclosed in document A9 and were therefore not suitable in demonstrating an improved efficacy or reduced toxicity of anti-NGF antibodies *vis-à-vis* vincristine in the claimed therapeutic application. Furthermore, document A9 did not disclose data comparing the efficacy of vincristine with that of morphine in alleviating bone cancer pain. Thus, the disclosed improved efficacy of an anti-NGF antibody compared to morphine in the patent was not suitable to indirectly support an alleged improved potency of these antibodies *vis-à-vis* vincristine.

Document A14 differed from the subject-matter of claim 1 in that it did not disclose the use of anti-NGF antibodies in the claimed therapeutic application.

In view of missing evidence of beneficial effects over the closest prior art, the technical problem was the provision of an alternative therapy or of alternative NGF antagonists in the treatment of bone cancer pain.

The use of neutralising anti-NGF antibodies in the treatment of chronic pain was explicitly suggested in document A9 (see columns 22, 23 and 26 and claims 1 and 8). Thus, the replacement of vincristine by these antibodies in the claimed therapeutic application was obvious for the skilled person in the light of the teaching of document A9 on its own. There were also no reasons apparent that would have deterred the skilled person from doing so. Several prior art documents disclosed the efficacy of anti-NGF antibodies in the therapy of inflammatory pain (see document A6, page 20, lines 29 to 33), neuropathic pain (see document A7, abstract) and mechanically-induced pain (see document A28, abstract), and aspects of all these pain states were likewise involved in bone cancer pain (see patent, paragraphs [0009] and [0047], and documents A29, page 404, sentence bridging columns 1 and 2, and A38, abstract). Furthermore, document A14 explicitly suggested NGF's involvement in bone cancer pain (see abstract). Lastly, the fact that certain prior art documents did not disclose NGF as a potential target in bone cancer pain did not constitute evidence that the skilled person would not have considered it as a target, since other reasons might have prevented the authors from mentioning NGF.

Admission of auxiliary requests 1 and 2 into the appeal proceedings

Auxiliary requests 1 and 2 filed by appellants I during the oral proceedings should not be admitted. The argument that the technical problem in view of the closest prior art was the provision of an alternative therapy or of an alternative NGF antagonist in the claimed therapeutic application instead of an improvement had already been raised in the opposition proceedings and in appellants II and III's statements of grounds of appeal. Therefore appellants I had had sufficient opportunities to address this issue earlier, which was also proven by the fact that auxiliary requests 7 and 8 had been filed in reply. Moreover, it was not apparent how the amendments would overcome the objection of lack of inventive step. Finally, the requests raised issues of clarity.

X. Appellants I requested that the decision under appeal be set aside and that the patent be maintained as granted, or alternatively that it be maintained in amended form on the basis of the claims of auxiliary request 1 or 2 filed during the oral proceedings.

Appellants II and III requested that the appeal of appellants I be dismissed and that the decision under appeal be set aside and the patent revoked.

Reasons for the Decision

1. The appellants' appeals are admissible.

Introduction to the invention

2. The present invention concerns the use of an antagonist of nerve growth factor (NGF) in the treatment of bone cancer pain.

3. NGF belongs to the neurotrophin protein family. Its members induce the development of neurons and are important for their survival and proper functioning. A binding of NGF to either the membrane-bound trkA tyrosine kinase receptor or the p75 receptor, the latter being structurally related to proteins of the tumour necrosis factor receptor family, causes an upregulation of neuropeptides in sensory neurons (see patent, paragraph [0002]).

4. Antagonists are agents that directly or indirectly result in decreased biological activity of molecules of interest, in the present case NGF (see paragraph [0014] of the patent).

Main request

Inventive step (Articles 100(a) and 56 EPC)

Closest prior art

5. For assessing whether or not a claimed invention meets the requirements of Article 56 EPC, the boards of appeal normally apply the "problem and solution"

approach. This requires as its first step the identification of the closest prior art. This is generally a prior art document disclosing subject-matter conceived for the same purpose or aiming at the same objective as the claimed invention and having the most technical features in common, i.e. requiring the minimum of structural modifications (see Case Law of the Boards of Appeal, 8th edition 2016 (hereinafter "CLBA"), I.D.3.1).

6. Appellants I considered the disclosure of document A9, appellants II and III that of either A9 or A14, as the closest prior art for the subject-matter of claim 1.

7. Document A9 discloses the administration of at least one local anaesthetic as sympathetic nerve blocker in a first step, followed by the administration of at least one antagonist of NGF to nullify its stimulatory activity on neurons in the treatment of sympathetic nerve-mediated chronic pain in human patients (see column 5, lines 8 to 23; column 11, line 62, to column 12, line 11; column 15, lines 14 to 17). Disclosed states of chronic pain to be treated are *inter alia* associated with neoplastic diseases (see column 13, lines 3 to 10).

7.1 The document reports, in relation to the processes causing chronic pain, that the uptake of excess NGF at the local site of injury "*begins the vicious, repetitious cycle of events causing the development and stage progression of chronic pain*" (see column 11, lines 14 to 20). In this context, it teaches that NGF "*is taken up by specific receptors in the axons of sympathetic fibers and sensory fibers and is transported up the fiber in retrograde fashion to the neural cell body*" (see column 10, lines 34 to 37) and

that the "*excess production of nerve growth factor then stimulates the neuron cell body into a hyperactive state; and the continued excess production of nerve growth factor will cause a repeated and increasing stimulation effect and hyperactivity of both sympathetic neurons and somatic sensory neurons*" (see column 10, lines 62 to 68). Lastly, the document reports that NGF's stimulation of neurons "*will continue indefinitely until the nerve growth factor itself is removed or nullified by an antagonist*" (see column 11, lines 8 to 13).

7.2 Document A9 discloses four categories of NGF antagonists. Firstly, it mentions vinca alkaloids, for example vincristine, which "*prevent the retrograde axonal uptake of nerve growth factor along the nerve fiber in-vivo*" (see column 22, lines 60 to 66, column 24, line 29); secondly, colchicine that acts by *inter alia* inhibiting superoxidation and cell growth (column 22, line 66, to column 23, line 3; column 25, lines 12 to 18); thirdly, polyclonal and monoclonal anti-NGF antibodies that neutralise the activity of NGF (see column 23, lines 3 to 8; column 26, lines 12 to 31); and fourthly, guanethidine, reserpine and 6-hydroxydopamine, which function as inactivators of sympathetic neurotransmitters (see column 23, lines 8 to 13; column 25, lines 49 to 55).

7.3 Furthermore, the document reports on four clinical studies involving human patients suffering from various chronic pains. "*Case History 1*" and "*Case History 2*" disclose two patients affected by a severe pain originating from multiple myeloma located either in the "*lower lumbar spine and sacrum*" (see column 27, lines 32 to 39) or "*in all his bones*" (see column 28, lines 19 and 20). It was common ground between the parties

that these disclosures meant that both patients suffered from a chronic bone cancer pain. The patients are treated by administering vincristine after having first received local anaesthetics to block their sympathetic nerves. After the treatment, the patients are reported to be either "*essentially pain free*" after nine months or "*relatively pain free*" one week later (see column 27, line 53, to column 28, line 27).

8. Document A14 discloses that NGF is involved in sensitisation in a variety of chronic pain states. It reports that NGF is strongly expressed *in vitro* in the murine osteolytic sarcoma cell line 2472, which expression continues *in vivo in mice that had received intramedullary injection of these cells into the femur*. Furthermore, the document reports that in these mice calcitonin gene-related peptide (CGRP)-immunoreactive nerve fibres are surrounded by cancer cells in tumour-bearing mouse femora. It states that the majority of these fibres are sensitive to NGF and therefore suggests that NGF "*may at least in part be responsible for the sensitization of a subpopulation of primary afferent fibers in bone cancer pain*" (see abstract). However, document A14 does not disclose an actual treatment of bone cancer pain.

9. Hence, only document A9 relates to the same purpose as that underlying the claimed invention, i.e. a treatment of bone cancer pain. Accordingly, the board concludes, in accordance with the criteria established by the case law (see point 5 above), that the administration of a local anaesthetic followed by the administration of vincristine in the treatment of chronic bone cancer pain disclosed in "*Case History 1*" and "*Case History 2*" in document A9 represents the closest prior art.

Technical problem and solution

10. Appellants I submitted that the subject-matter of claim 1 differed from the closest prior art treatment disclosed in document A9 in using an antagonistic anti-NGF antibody instead of vincristine. This antibody specifically targeted NGF without harming sensory neurons, which were certainly damaged by vincristine's neurotoxic activity. Furthermore, it was submitted that the patent demonstrated that the pain-relieving efficacy of an anti-NGF antibody in the claimed therapeutic application was increased compared to that achieved with morphine, a further notable improvement over the findings in document A9.

11. The patent discloses in examples 2 and 3 that an anti-NGF antibody has a superior efficacy compared to morphine in alleviating pain in a mouse model of bone cancer (see paragraphs [0188], [0201], [0209], [0224]) and that the anti-NGF antibody does not cause significant adverse side-effects under these conditions (see e.g. paragraph [0226]). However, the patent does not disclose a comparison of the efficacy or the potential toxicity of vincristine and an anti-NGF antibody in the same model system.

12. Accordingly, the patent does not disclose results which can be compared directly with the results in the closest prior art document A9, and this has actually not been argued by appellants I.

13. Accordingly, in view of these considerations the board is of the opinion that the results in the patent do not demonstrate a more potent effect or a reduced toxicity of the anti-NGF antibody over vincristine in the treatment of bone cancer pain and that therefore no

case for improved effects over the effects in the closest prior art has been established.

14. Thus, the objective technical problem to be solved is the provision of an alternative means in the treatment of bone cancer pain.

15. The board is satisfied that the subject-matter of claim 1 solves this technical problem in view of the demonstrated efficacy of the antagonistic anti-NGF antibody in the claimed therapeutic application in the patent (see point 11 above).

Obviousness

16. It has to be assessed whether or not the skilled person, starting from the administration of a sympathetic nerve blocker followed by the administration of vincristine in the treatment of bone cancer pain as disclosed in document A9 and faced with the technical problem defined above, would arrive in an obvious manner at the use of an antagonistic anti-NGF antibody as an alternative to vincristine.

17. Document A9 teaches that: "*Blockade of the sympathetic nerve tract alone using local anesthetics is by necessity short-term if effective and is efficacious only in early distrophies. Investigative research by other has shown that NGF blockade percutaneously can also be efficacious, but the method requires long-term, repeated applications. The present invention maintains that sympathetic blockade coupled with NGF antagonism by any effective means act together to produce far more efficacious and longer lasting relief from chronic pain*" (see column 11, lines 35 to 44, emphasis added). Accordingly, the document discloses as a generic

concept the central role of NGF antagonists in achieving long-term effects in the treatment of chronic pain. In this context bone cancer pain and vincristine's function as an NGF antagonist are explicitly disclosed (see points 7 and 7.3 above).

18. The skilled person seeking for alternative means in the treatment of bone cancer pain would in the same document have encountered Section C, headed "*Administering An Antagonist Of Nerve Growth Factor To The Living Subject Whereby The Administered Antagonist Substantially Nullifies The Neuron Stimulation Effect Caused By Such Nerve Growth Factor As Is Present*" (see column 22, lines 34 to 39), where, in relation to NGF antagonists, the following is disclosed: "*A third category is represented by the known polyclonal or monoclonal anti-nerve growth factor antibodies conventionally known and described in the literature which are recognized as being able to neutralize nerve growth factor molecules directly upon reactive contact*" (see column 23, lines 3 to 8).

19. Since anti-NGF antibodies that neutralise NGF's stimulation of neural cells are explicitly mentioned in document A9 as NGF antagonists in the treatment of chronic pain, the board considers that the above-cited passages provided the skilled person with a direct incentive to contemplate their use in the treatment of patients suffering from bone cancer pain as an alternative to vincristine in the treatment.

20. Appellants I argued that the skilled person reading in particular the clinal study "*Case History 1*" in document A9 and taking common general knowledge into account would have had doubts that vincristine's reported effect in reducing chronic bone cancer pain

was in fact mediated by an antagonism of NGF. This was so because the agent was known for its cytotoxic effects on neurons (see document A48, page 1419, column 1, third paragraph) and tumour cells (see document A9, column 4, lines 9 to 16). Both of these effects of vincristine were rather long-lasting, which seemed to match with the patient's reported pain-free state nine months after concluding the treatment.

In contrast thereto had any potential antagonising effect of vincristine on NGF to be relatively short in view of the reported administration for only four days (see Case History 1) and its known short half-life of about 20 hours (see document A48, page 1418, column 1, last paragraph). It followed from this that the skilled person would have had doubts that NGF itself was even a suitable target in treating bone cancer pain, in particular since results with other NGF antagonists were lacking in document A9.

20.1 The board notes that it is common ground between the parties that the skilled person reading document A9 is aware of vincristine's multiple effects *in vivo*, i.e. its cytotoxicity on neurons and cancer cells, and that it reduces chronic pain, including bone cancer pain (see column 4, lines 5-6 and 20-21, column 25, lines 9 to 11, and Case Histories 1 and 2).

20.2 Therefore, in the board's view, the skilled person has no reason to assume that vincristine's reported efficacy in reducing bone cancer pain in document A9 solely relies on only one of these effects, namely cytotoxicity. With regard to vincristine's relatively short biological half-life, the board notes that appellants I argued that the mechanisms underlying bone cancer pain and its transmission were unknown to the

skilled person at the relevant date of the patent. In this situation, in the board's opinion, the skilled person would not have speculated whether short-term or long-term effects of vincristine were responsible for its reported reduction of bone cancer pain, since in the absence of any information both appear to be equally probable.

20.3 Furthermore, as set out in point 17 above, the central teaching of document A9 is directed to NGF as the target in chronic pain, and consequently NGF antagonism as the appropriate therapeutic approach. In line with this, document A9 reports that vinca alkaloids, e.g. vincristine, "*function as blocking agents* [of NGF, comment added by the board] *and prevent the retrograde axonal uptake of nerve growth factor along the nerve fiber in-vivo*" (see column 22, lines 63 to 66).

20.4 In view of these considerations the board is not convinced by appellants I's arguments.

21. In a further line of argument, appellants I submitted that bone cancer pain was a unique state of pain, since (i) analgesics that reduced inflammatory or neuropathic pain were often ineffective in its therapy and (ii) it induced a biochemical signature in neurons not seen in other pain states. Therefore, the skilled person reading document A9 would not have derived therefrom that NGF was a target at all in the treatment of bone cancer pain. The same applied to the prior art, since the documents cited suggested many potential target proteins, but not NGF. Furthermore, in view of the demonstrated clinical and biochemical uniqueness of bone cancer pain, the skilled person had no reasonable expectation that the anti-NGF antibody was therapeutically effective.

22. The board is not convinced by these arguments either, since, as set out in points 7.1 to 7.3 above, document A9 explicitly discloses that NGF is a central target in bone cancer pain and that vincristine as an NGF antagonist is effective in treating it. The involvement of NGF is also explicitly suggested in document A14 (see point 8 above). Moreover, the fact that some of the cited prior art documents do not mention NGF as a potential target in the claimed therapeutic application does not on its own constitute evidence that the skilled person would have disregarded it, least of all in the present case, where evidence and indications for NGF's involvement are available, while evidence or indications to the contrary are lacking.

23. In view of the above considerations, the board concludes that the subject-matter of claim 1 of the main request lacks an inventive step with regard to the disclosure of document A9 on its own and that this ground for opposition therefore prejudices the maintenance of the patent as granted (Articles 100(a) and 56 EPC).

Admission of auxiliary requests 1 and 2 into the proceedings (Article 13(1) RPBA)

24. The filing of the claims of auxiliary requests 1 and 2 by appellants I during the oral proceedings represented an amendment to appellants I's case within the meaning of Article 13(1) RPBA. The admission of these requests into the proceedings and their consideration were therefore at the board's discretion.

25. The claim requests were presented at the oral proceedings and thus at a very late stage in the appeal proceedings.

26. According to appellants I the requests were submitted specifically to address the board's finding under Article 56 EPC that the objective technical problem was the provision of an alternative and not of an improved treatment in bone cancer pain and were filed immediately once the board's opinion was known.

27. However, the board notes that the objection pursuant to Article 56 EPC, including the consideration that, having regard to the disclosure in document A9, the technical problem should be formulated in a less ambitious manner, namely as the provision of an alternative, had already been raised by opponent 01 in the first-instance proceedings (see contested decision, point 38 of the reasons) and has been retained by both appellants II and III in their statements of grounds of appeal (see page 6, third paragraph, of appellant II's letter dated 21 May 2013 and point 4.13 of appellant III's letter dated 24 May 2013, respectively). Appellants I must thus have already been aware of that objection when filing their statement of grounds of appeal or their reply to appellants II and III's statements of grounds of appeal. That the board might follow appellants II and III's approach was one of the two possible scenarios, but cannot be held to be unforeseeable. Also, no new objection was raised *ex officio* by the board and no new line of objection was raised by appellants II and III during the oral proceedings (see CLBA, IV.E.4.4.12). Therefore, in the present case, the board cannot conclude that an unexpected development of the case occurred that may have justified the late filing of auxiliary requests 1 and 2.

28. Furthermore, the claims filed as auxiliary requests 1 and 2 were amended in such a way as to include new features taken from the description. These amendments raised further issues, in particular objections as to clarity pursuant to Article 84 EPC as argued by appellant II, and were directed to subject-matter which had not been previously addressed in the appeal proceedings. This would have added further complexity to the case and led to a discussion of entirely new aspects for the first time at the oral proceedings before the board.

29. Based on the above considerations, the board decided not to admit auxiliary requests 1 and 2 into the proceedings pursuant to Article 13(1) RPBA.

Order

For these reasons it is decided that:

1. The appeal of appellants I is dismissed.

2. The decision under appeal is set aside.

3. The patent is revoked.

The Registrar: The Chairwoman:

D. Hampe G. Alt

Decision electronically authenticated